REMARKS

Claims 1-15 were pending before the Examiner in the present Office Action of the instant application. Claim 1 has been amended. Claim 3 has been canceled. Accordingly, claims 1, 2, 4 and 5 will remain pending upon entry of the amendments presented herein. Claims 6-15 are withdrawn as allegedly not being drawn to the elected invention.

Support for the amendments to the claims can be found throughout the specification and claims as originally filed. No new matter has been added to the application.

The foregoing amendments have been made solely to claim more fully the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in one or more subsequent applications.

Further, it is respectfully submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as the changes place the application in condition for allowance.

A. The rejections under 35 U.S.C. § 112, first paragraph, are overcome

Enablement

The Office Action rejects claims 3 and 4 under 35 U.S.C. § 112, first paragraph, for allegedly lacking an enabling disclosure. The Office Action states that "the teaching of the specification cannot be extrapolated to enable the claims because one of skill in the art could not predict that the invention would function as claimed. In particular, the teaching in the specification is not sufficient to establish that a Raf kinase inhibitor would have an affect on adrenomedullin RNA levels in tumors in vivo because of the art recognized differences between

tumor cells derived from a cell line and tumor cells in an in vivo tumor." See Office Action, page 4, lines 7-12. The Office Action then turns to several references in support of its conclusion. Taken together, the references generally acknowledge that there are differences between cultured cancer cells and their counterpart cancer cells in vivo and that animal models are not the perfect predictors for the success of anti-cancer drugs in humans. The Examiner's contention is that "based on cell culture data it could not be predicted that, in the in vivo environment, the invention would function as claimed." See Office Action, page 5, lines 4-5.

Applicants respectfully disagree with the Office Action and traverse the rejection.

It is respectfully submitted that the Office Action is improperly focused only on a single factor in the test set forth by *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), namely, the predictability factor. Moreover, the Office Action's conclusion that the present invention "would [not] function as claimed" due to a lack of predictability in extrapolating the "cell culture data" of the application to the claimed in vivo method is directly contrary to the case law of the Federal Circuit, e.g. see *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (holding that proof of an alleged pharmaceutical property for a compound by statistically significant animal tests is sufficient to reasonably predict the success of the compound in humans). Therefore, the Examiner's rejection simply does not follow the guidelines set forth by the Federal Circuit and thus, must fail.

According to the Federal Circuit in *In re Wands*,

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Id. at 1404.

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands*. For example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance

presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Here, the Office Action focuses exclusively on the predictability or unpredictability of the art. None of the other factors are considered. The Office Action primarily cites several references to support the notion that because the art recognizes many differences between cultured cells and their in vivo counterparts, a specification having only cell-culture based data would not allow one of ordinary skill in the art to reasonably predict the success of the claimed in vivo method.

As an initial matter, it appears that the Office Action characterizes the data of the present specification to be limited to in vitro cell culture data. This is simply not the case. To clarify, the present application supports the presently claimed method with four examples, none of which describe in vitro cell culture data. Instead, Example 1 describes a mouse tumor xenograft model used to test the effect of a Raf kinase inhibitor compound on human pancreatic and lung tumors implanted into the test mice. While the human cancers are originally derived from tissue culture, the experiment involves testing the compound in an in vivo environment, i.e. a xenograft model. Accordingly, the data of the application goes beyond in vitro tissue culture analysis of test compounds, contrary to what seems to be implied in the Office Action.

Even if, arguendo, the Office Action based the rejection on the alleged unreliability of the xenograft mouse data of the application, the rejection is still deemed to be improper. In fact, the rejection is in direct contradiction to the Federal Circuit's decision in *In re Brana*.

In *In re Brana*, the Federal Circuit heard on appeal a decision of the Board of Patent Appeals and Interferences which affirmed the patent examiner's rejections under 35 U.S.C. § 112, enablement, of claims directed to antitumor compounds and their use as effective anti-tumor substances. During prosecution, the examiner had rejected the claims under 35 U.S.C. § 112, enablement, on the basis that the *in vivo* mouse tests were insufficient to establish a reasonable expectation that the claimed compounds possessed an antitumor activity in humans. In explaining the Patent Office's position, the court stated that "the Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed

compounds for treating cancer in humans." The court reminded the Commissioner that the Patent Office is not the Food and Drug Administration, stating that "the Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining governmental approval to market a particular drug for human consumption." The court cited precedent that "testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings."

Applicants are faced with the same rejection as in *In re Brana*. In the present application, the Examiner similarly rejected the claims as allegedly lacking enablement on the basis that the disclosed *in vivo* mouse model data is allegedly insufficient to establish reasonable predictability of the effectiveness of the anticancer compounds in humans. In other words, the Examiner, on the basis of the mouse model data, doubted that the "invention would function as claimed." It would appear that to the Examiner, like in *In re Brana*, some kind of human data would be necessary to satisfy the requirements of Section 112. Thus, like in *In re Brana*, the Patent Office would appear to be playing the role of the FDA—thereby imposing the wrong standards on the applicants as to the nature of experimental support needed to show that the invention would indeed function as claimed. As noted by the Federal Circuit, if FDA testing were required to meet the requirements of 35 U.S.C. § 112, "the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue through research and development, potential cures in many crucial areas such as the treatment of cancer."

Accordingly, the rejection is clearly improper on the basis of *In re Brana* and should be reconsidered and withdrawn.

Turning to the other factors of *In re Wands*, Applicants respectfully point out that the Office Action improperly fails to consider factors other than the predictability or unpredictability of the art. The M.P.E.P. states that "it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above [*Wands*] factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole." See M.P.E.P. 2164.01(a)(bracketed matter added).

While the Office Action contends—albeit only cursorily—that Applicants' specification does not include any working examples (see Office Action, page 5, line 14-15), this conclusion is incorrect as Applicants' disclosure includes at least one working example. Example 1, as discussed above, relates to a mouse xenograft model study which tests the effects of certain anticancer compounds on human cancers implanted into mouse models. According to the M.P.E.P., "an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention." See M.P.E.P. 2164.02. Here, the mouse model data "correlates" with the claimed invention, *inter alia,* because the data demonstrate that the level of expression of a biomarker (adrenomedullin) is a useful marker to show the effectiveness of an anticancer treatment. Moreover, as noted by *In re Brana*, such mouse models are "widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound" and thus, are accepted modes of testing compound effectiveness for use in humans. *In re Brana*, 51 F.3d at 1563.

Accordingly, enablement clearly exists when proper consideration is given to each and every factor in *In re Wands*. The claimed methods, as presently amended herein, are diagnostic by nature, and extensive guidance for conducting the methods is provided by the specification, including several examples. Thus the amount of direction and guidance is high. In addition, the level of skill among practitioners in the art is high. This factor necessarily tips in favor of the Applicants since the extent of guidance necessary is indirectly proportional to the degree of skill. Thus, the high degree of skill favors less, rather than more, guidance. Moreover, *In re Brana* demonstrates that the factor involving the predictability of the arts favors Applicants. Therefore, given the teachings of the specification, the quantity of experimentation and guidance, the high degree of skill, and the lack of unpredictability in the art, undue experimentation by such practitioners is not required. As stated in MPEP 2164.01, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Accordingly, it is respectfully submitted that adequate guidance is provided to enable the skilled artisan to practice the claimed invention without undue experimentation. Therefore,

reconsideration and withdrawal of the U.S.C. § 112, first paragraph rejections are earnestly solicited.

Written description

The Office Action rejects claim 3 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Specifically, the Office Action contends that specification "does not provide the complete structure of any Raf kinase inhibitors, nor does the specification provide any partial structure of such Raf kinase inhibitors, nor any physical or chemical characteristics of Raf kinase inhibitors, nor any functional characteristics coupled with a known or disclosed correlation between structure and function, other than the description of the Raf kinase inhibitor, ISIS 5132, a phophorothioate antisense oligonucleotide." The Office Action concludes that such a lack of description fails the standards for written description set forth by the Federal Circuit in *University of California v. Eli Lilly*, 119 F.3d 1159 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002).

Applicants respectfully disagree with the rejection and traverse as follows.

That the present application may not describe particular Raf kinase inhibitors or their structures in no way violates existing law of the Federal Circuit pertaining to written description. The court recently decided in *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006) that Federal Circuit precedent, including *Eli Lilly*, did not set a *per se* rule that structural descriptions of claimed molecules were required to meet the written description requirements and that no such description is required where "accessible literature" provides for such information. This holding is also consistent with the earlier court decision in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986) which held that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.

Turning more closely to *Falkner*, the Federal Circuit heard an appeal from a decision of the Board of Patent Appeals and Interferences (the "Board") in an interference between Falkner et al. and Inglis et al., in which the Board entered judgment against Falkner. The court affirmed the Board's decision, thereby awarding priority and a right to a patent to Inglis. *Id.* at 1358. The interference count at issue before the Board related to a poxvirus vaccine that was made attenuated through the deletion or inactivation of an *essential* gene for the purposes of providing a safer vaccine than had been available previously. Up until the time of the invention, the art pertaining to the attenuation of poxviruses involved the inactivation of only *inessential* genes.

Such art-known attenuated virus vaccines were disadvantaged in that they "could still cause a harmful infection in the inoculee." *Id.* At 1360.

The interference count particularly related to mutant poxvirus vaccines having "a genome which has an inactivating mutation in a viral gene, said viral gene being essential for the production of infectious new virus particles," i.e. an *essential* gene. *Id.* At 1360. During the interference proceedings, the Board reviewed three motions by Falkner which separately challenged the patentability of the Inglis claims on the grounds of lack of written description, lack of enablement, and anticipation. *Id.* At 1362-1363. On appeal, the court combined the issues presented by Falkner before the Board into one central issue, namely "whether the Inglis benefit applications [i.e. the priority applications] adequately describe and enable a poxvirus-based vaccine." *Id.* At 1363.

The court held the following as being consistent with the current law of written description: "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and **(3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure."** *Id.* at 1366. Further, the court in considering whether Inglis's failure to provide any DNA sequences of the poxvirus genome or the locations of the "essential" genetic regions to be deleted should fail the written description requirement, held that no such disclosure was required because the sequences were already known in the art. *Id.* at 1367.

The court especially noted that "it is the binding precedent of this court that *Eli Lilly* does *not* set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art." *Id.* at 1367. The court explained that "a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement," and held that "**where...accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences."** *Id.* at 1358 (emphasis added).

The facts and issues in *Falkner* are similar to those raised by the rejections of the present Office Action. It is respectfully submitted that the holdings of *Falkner* necessitate

reconsideration and withdrawal of the rejections under 35 U.S.C. § 112 since numerous Raf kinase inhibitors are known and described in the art. See, for example, Raf kinase inhibitors described in U.S. Patent No. 7,071,216, which also incorporates by reference the Raf kinase inhibitors described in (a) Crump, Current Pharmaceutical Design, 2002, 8:2243-2248, (b) Sebastien et al., Current Pharmaceutical Design, 2002, 8:2249-2253, (c) Kolch et al., Nature, 1991, 349:416-428, (d) Monia et al., Nature Medicine, 1996, 2:668-675, and (e) U.S. Patent Nos. 6,458,813, 6,391,636, 6,358,932, 6,268,391, 6,204,467, 6,037,136 and 5,717,100. Accordingly, under *Falkner*, Applicants should not be required to have disclosed particular Raf kinases or their structures in order to fulfill the requirements of written description.

Moreover, by requiring particular Raf kinase inhibitors or their structures to have been disclosed in the specification misses the point of the invention. The present invention is directed to a method of monitoring the response of a patient being treated for cancer by administering a Raf kinase inhibitor and examining the expression level of a biomarker over time to assess its effectiveness. Any Raf kinase inhibitor—those already known and those that may be developed in the future—are within the scope of the presently claimed invention. Applicants are entitled to this scope because the fundamental discovery of the invention is that the expression of certain biomarkers, e.g. adrenomedullin, are regulated by Raf kinases. The inventors, in other words, discovered an important and significant link between inhibiting a Raf kinase and the effect on the biomarkers of the invention. As taught in the present application, it was already known at the time of the invention that inhibition of Raf kinase was an important target for cancer therapy (see e.g., paragraph 4-5 of the published application, US 2004/0121375 A1)—what was needed in the art was a way to effectively monitor the efficacy of treatment with Raf kinase inhibitors (see e.g., paragraph 7 of the published application). Accordingly, it matters not so much which Raf kinase inhibitor is used, but rather whether there is inhibition of a Raf kinase—the extent of which can be assessed by the expression level of the inventive biomarkers. Thus, any Raf kinase inhibitor can be used so long as the change in the level of expression of the biomarker can be detected in the way that is claimed in the present invention.

Accordingly, in view of the above, it is believed that the presently claimed invention meets the requirements under 35 U.S.C. § 112, first paragraph—written description. Reconsideration and withdrawal of the Section 112 rejections are respectfully requested.

B. The rejections under 35 U.S.C. § 102 are overcome

The Office Action rejects claims 1-2 and 5 under 35 U.S.C § 102(b) as allegedly being anticipated by Ebert et al. ("Monitoring of therapy in inoperable lung cancer patients by measurement of CYFRA 21-1, TPA-TP CEA, and NSE," Anticancer Research, 1997, 17:2875-8, Abstract only) (hereinafter as "EBERT"). Applicants disagree with the conclusions of the Office Action and respectfully traverse as provided below.

The present invention broadly relates to biomarkers, e.g. adrenomedullin, and methods of using biomarkers for diagnosing and monitoring cancer in a patient, e.g. monitoring tumor progression and differentiation. The biomarkers of the invention can also be used in the screening and evaluation of anti-cancer compounds, e.g. Raf kinase inhibitors. As presently claimed, the present invention is directed to a method to monitor the response of a patient being treated for cancer by administering a Raf kinase inhibitor, comprising the steps of: (a) determining the level of expression of one or more one biomarker(s) in a first biological sample taken from the patient prior to treatment with the Raf kinase inhibitor; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the Raf kinase inhibitor; and (c) comparing the level of expression of the biomarker in the second biological sample with the level of expression of the biomarker in the first biological sample; wherein a change in the level of expression of the biomarker in the second biological sample compared to the level of expression of biomarker in the first biological sample indicates that the effectiveness of the treatment with the Raf kinase inhibitor. In a further claimed aspect, the biomarker is adrenomedullin.

The Examiner is respectfully pointed to the M.P.E.P § 2131 which states that "[a] claim is anticipated **only if each and every element** as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). Moreover, the prior art must contain an enabling disclosure for a Section 102 rejection to stand. *See Chester v.* Miller, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). "A claimed reference cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See, e.g. Id.* At 1354 and *In re Donohue,* 226

U.S.P.Q. 619, 621 (Fed. Cir. 1985). "The disclosure must be such as will give possession of the invention to the person of ordinary skill; even the act of publication or the fiction of constructive reduction to practice will not suffice if the disclosure does not meet this standard." *See In re Borst,* 345 F.2d 851, 855 (CCPA 1962).

Respectfully, the following explanation will show that EBERT does not teach, either expressly or inherently, each and every element of the presently claimed invention. Moreover, EBERT does not contain an enabling disclosure sufficient to have placed a person of ordinary skill in possession of the invention. Accordingly, the rejections under Section 102 should be reconsidered and withdrawn.

EBERT relates to a study of 381 lung cancer patients who have been administered an undisclosed (based on the contents of the cited abstract) form of cancer therapy. The study evaluated whether specific commonly-known tumor markers (CYFRA 21-1, TPA-M, TPS, CEA and NSE) had "the potential to contribute to clinical decision-making processes with respect to diagnosis and assessment of response to therapy." The study found that the use of the markers was "clearly inferior to the yield of standard cytopathological examinations" and concluded that the tested markers "are of minor value in the primary diagnosis of lung tumors."

EBERT clearly does not teach each and every element of the present invention. For example, the presently claimed invention is directed to monitoring the response of a patient particularly to Raf kinase inhibitors. EBERT does not recite any particular treatment or compound or therapy that includes Raf kinase inhibitors. Accordingly, EBERT does not teach each and every feature of the claims.

Even if, arguendo, EBERT did teach treatment with Raf kinase inhibitors, EBERT does not constitute an enabling disclosure and thus, is not a proper reference under Section 102. "The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter." MPEP § 2121.01. The evidence of lack of enablement, and even still, inoperability, comes from EBERT itself. EBERT effectively concedes that its biomarkers are <u>not</u> reliable or predictive in the diagnosis or evaluation of the effectiveness of its administered therapy. In its own words, the study found that the use of the markers was "clearly inferior to the yield of standard cytopathological examinations" and concluded that the tested markers "are of minor value in the primary diagnosis of lung tumors." Certainly, such data showing the inoperability and failure of certain well-known markers to be used in diagnosing cancer or

measuring treatment effectiveness would not place the presently claimed method in the possession of one of ordinary skill in the art.

Accordingly, as EBERT does not teach, either expressly or inherently, each and every element of the presently claimed invention nor does it provide enabling disclosure, the Section 102 rejection cannot stand. Reconsideration and withdrawal of the Section 102 rejection are respectfully requested.

REQUEST FOR AN INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the foregoing amendments and remarks presented herein, reconsideration and withdrawal of all rejections and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney(s) would help to expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned.

Respectfully submitted,

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